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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

20583 7590 12/15/2003

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed September 19, 2003.

Claims 1, 12, 16, 19, 20, 21, 22, 23, 29, 30, and 31, have been amended.

Claims 1-23 and 29-33 are pending in the instant application.

Information Disclosure Statement

The Information Disclosure Statements, filed December 17, 2002 and September 19, 2003 are acknowledged. The references referred to therein have been considered on the merits.

Nucleotide and/or Amino Acid Sequence Disclosure

Applicants Amendment to the Specification to comply with the Sequence Rules is acknowledged.

Priority

Applicants Amendment to the Specification to include priority information is acknowledged.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 12, 19, 29 and 30 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicants arguments that the Specification defines the term "reduced dose".

Claim Rejections - 35 USC § 102

Claims 1-5 and 13-18 were rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al., (The Lancet, 1997 Vol. 349:1137-1141). **This rejection is maintained** for the reasons of record set forth in the previous office action of March 18, 2003.

Applicants argue that the Webb reference does not anticipate the claimed invention because Webb does not describe the treatment or prevention of cancer through the administration of a bcl-2 antisense oligomer for any period of time less than 14 days, and therefore does not anticipate the presently claimed invention in which bcl-2 antisense oligomer is administered in cycles of 2 to 13 days. This is not found persuasive because claim 1 has been amended to include "each cycle of therapy comprising...". The term "comprising" is open language and includes, in this case, 2 to 13 days, plus an additional step(s). The therapy of Webb comprises 2 to 13 days, plus the additional step of one day, totaling 14 days, and therefore anticipates the claims.

Applicants argue that in Webb, therapy consists of a single two-week course of treatment (i.e. 14 days). This is not found persuasive because the therapy of Webb et al. does not consist of a single treatment, but instead consists of a daily treatment for 14 days (see page 1137.

Methods, first sentence). Applicants argue that one of more cycles of therapy, each lasting 2 to 13 days, is novel over Webb, because a cycle of therapy lasting 14 days cannot "encompass" a cycle of therapy lasting between 2 to 13 days. This is not found persuasive because the therapy of Webb et al. consists of one or more cycles of therapy, each lasting 2 to 13 days. For example, Webb et al. administered two cycles of therapy, each lasting 7 days and totaling 14 days.

Therefore, Webb et al. anticipates claims 1-5 and 13-18.

Claim Rejections - 35 USC § 103

Claims 1, 6-11 and 13-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Jansen et al. (Proceedings of the American Society of Clinical Oncology, 1999 Vol. 19:531a). **This rejection is maintained** for the reasons of record set forth in the previous office action of March 18, 2003.

Applicants argue that Webb describes only a bcl-2 antisense oligomer therapy regimen that lasts for a period of 14 days. Applicants further argue that Jansen describes a clinical study in which a bcl-2 antisense oligonucleotide was administered at a dose of between 0.6-2.3 mg/kg/day, also for 14 days, to patients with malignant melanoma, in combination with a standard dacarbazine regimen. Applicants argue that Webb and Jansen, taken alone or in combination, do not teach or suggest administering a bcl-2 antisense oligonucleotide in a treatment cycle consisting of less than 14 days (i.e., 2 to 13 days). This is not found persuasive because claim 1 includes the term "comprising". The term comprising is open language and includes, in this case, 2 to 13 days, plus an additional step(s). The therapy of Webb comprises 2 to 13 days, plus the additional step of one day, totaling 14 days, and therefore anticipates the

claims. Further, the therapy of Webb et al. consists of one or more cycles of therapy, each lasting 2 to 13 days. For example, Webb et al. administered two cycles of therapy, each lasting 7 days and totaling 14 days. Jansen et al. teach bcl-2 antisense oligonucleotide therapy combined with therapeutic agents, such as dacarbazine, are a novel and rational approach to improve response to chemotherapy in patients with cancer (see Abstract).

Therefore, it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide daily for 2 to 13 days and further administer one or more cancer therapeutics with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. because combined therapy of dacarbazine and bcl-2 antisense are a novel and rational approach to improve response to chemotherapy.

Claims 1, 6, 10, 12, 19 and 29-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., and Jansen et al. as cited in the 35 U.S.C. 103(a) rejection against claims 6, 9, 10 and 11 in further view of Klasa et al. (Clinical Cancer Research, 2000 Vol. 6:2492-2500). **This rejection is maintained** for the reasons of record set forth in the previous office action of March 18, 2003.

Applicants argue against Webb et al. and Jansen et al. as recited in the 35 U.S.C. 103(a) rejection against claims 1, 6-11 and 13-18 above. Further, Applicants argue that Klasa et al. disclose a study in which SCID mice with B-cell lymphoma were given a bcl-2 antisense

oligonucleotide 5 mg/kg/day (or every other day) for 14 total doses. Applicants argue that Klasa et al. do not teach or suggest a treatment cycle of 2 to 13 days as present claimed. This is not found persuasive because Webb et al. teach a treatment cycle of 2 to 13 days as described in the 35 U.S.C. 103(a) rejection against claims 1, 6-11 and 13-18 above. Klasa et al. was relied upon to teach the combined therapy of a bcl-2 antisense oligonucleotide with anticancer drug, cyclophosphamide. Klasa et al. further teach that improved clinical outcomes could be achieved with standard, or even lower doses of anticancer drugs when combined with antisense oligonucleotides, thus impacting overall clinical tolerance and costs of care (see page 2499, last paragraph).

Therefore, it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide daily for 2 to 13 days and further administer one or more cancer therapeutics with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Klasa et al. because combined therapy of cyclophosphamide and bcl-2 antisense improve clinical outcomes. One of ordinary skill in the art would have been motivated to lower the dose of the cancer therapeutic because Klasa et al. explicitly taught that improved clinical outcomes could be achieved with standard, or even lower doses of anticancer drugs when combined with antisense oligonucleotides, thus impacting overall clinical tolerance and costs of care.

Claims 19-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al., and Klasa et al., in further view of Tortora et al. (Antisense and Nucleic Acid Drug Development, 1998 Vol. 8:141-145); Adjei et al. (Seminars in Oncology, 1999 Vol. 26:32-40); Foran et al. (Journal of Clinical Oncology, 1999 Vol. 17:546-53); or Murren et al. (Caner Chemotherapy Pharmacology, 2000 Vol. 46:43-50). **These rejections are maintained** for the reasons of record set forth in the previous office action of March 18, 2003.

Applicants argue against Webb et al. and Jansen et al. as recited in the 35 U.S.C. 103(a) rejection against claims 1, 6-11 and 13-18 above. Applicants argue against Klasa et al. in the 35 U.S.C. 103(a) rejection against claims 1, 6, 10, 12, 19 and 29-33 above. Further, Applicants argue that Tortora et al. is relied upon for its teaching of paclitaxel dosing at 20 mg/kg; Adjei is relied upon for its teaching of docetaxel at 60-100mg/ m^2, Foran is relied upon for its teaching of fludarabine at 25 mg/m^2, and Murren is relied upon for its teaching escalating doses of irinotecan starting at 50 mg/ m^2. Applicants argue that none of these documents cure the failure of Webb et al. to teach or suggest a bcl-2 antisense treatment cycle of 2-13 days. Applicants argue that the total combination of references teaches only a 14-day treatment with bcl-2 antisense oligonucleotide and the standard dose of cancer therapeutic. This is not found persuasive because Webb et al. teach a treatment cycle of 2 to 13 days as described in the 35 U.S.C. 103(a) rejection against claims 1, 6-11 and 13-18 above. Tortora et al. Adjei et al. Foran et al. and Murren et al. were relied upon for teaching combination therapy of bcl-2 antisense oligonucleotides with chemotherapeutic drugs. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide daily

for 2 to 13 days and further administer one or more cancer therapeutics with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Klasa et al. because combined therapy of cyclophosphamide and bcl-2 antisense improve clinical outcomes. One of ordinary skill in the art would have been motivated to lower the dose of the cancer therapeutic because Klasa et al. explicitly taught that improved clinical outcomes could be achieved with standard, or even lower doses of anticancer drugs when combined with antisense oligonucleotides, thus impacting overall clinical tolerance and costs of care. One of ordinary skill in the art would have been motivated to administer the bcl-2 antisense oligonucleotide of Webb et al. with various, including lower doses of chemotherapeutic drugs taught by Tortora et al. Adjei et al. Foran et al. and Murren et al. since, at the time the invention was filed, it was well known in the art to administer combined therapy regimens and it was well known to range the chemotherapeutic drug dose to meet the maximal therapeutic benefit for a range of individuals.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 746-8693.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
December 9, 2003

KAREN A. LACOURCIERE
PRIMARY EXAMINER